Rheumatology Practice at Mayo Clinic: The First 40 Years–1920 to 1960

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In its early years, Mayo Clinic had primarily a surgical practice. Patients with musculoskeletal complaints were cared for by one of the Mayo brothers (Dr William J. Mayo or Dr Charles H. Mayo) or their initial partners. That such patients were seen in Rochester, MN, is evidenced by a report the brothers wrote in 1895 that described surgical treatment of a patient with knee sepsis.[1,2] A second article on this topic appeared 2 years later.[3]

In 1910, Dr Melvin S. Henderson was appointed to develop a Section of Orthopedics. To gain experience and become acquainted with the best orthopedic practices of the day, Henderson visited a number of leading orthopedists in the United States and was sent by the Drs Mayo to visit centers in Great Britain in 1911 and 1912. Dr Henry W. Meyerding joined Henderson in 1911.[4] Patients with bone and joint problems were then seen by Henderson and Meyerding.

The first nonsurgical physicians who joined Mayo Clinic functioned mainly to screen patients for surgery and participate in postoperative management (G. Eusterman, MD. My experience at the Mayo Clinic. Unpublished manuscript, 1956). As Mayo Clinic grew in size and reputation in the early part of the 20th century, the patient population evolved. Increasing numbers of patients were referred to Rochester or arrived on their own with a broad variety of illnesses, some not amenable to surgery. Thus, the need to diagnose and manage nonsurgical conditions continued to expand, and physicians with an interest in medical diseases were recruited. Additionally, hospital beds were dedicated to nonsurgical patients, initially in 1917 (G. Eusterman, MD).

Progress in medicine has evolved gradually throughout history. Even though a specific date can be provided for a new discovery, time is often required to confirm this finding and disseminate the advance to others. In the current report, we have attempted to determine when a medication, method, or practice was actually used rather than when it was first described. We have divided the history into 3 periods, which are general timelines rather than strict demarcations.

Mayo Clinic grew markedly during the 40 years between 1920 and 1960. In 1920 there were 62 medical staff members, and in 1960 there were 348.

1920-1940

Dr Phillip S. Hench, who became the first rheumatologist at Mayo Clinic, arrived in Rochester in October 1921 for training in medicine and surgery after graduating from the University of Pittsburgh Medical School in 1920.[5] He later stated that for a time he was the only resident primarily interested in training in internal medicine at Mayo Clinic.[6] In 1923, Hench was appointed as a first assistant in the Section of Medicine, headed by Dr Leonard Rowntree.[5] Dr William Mayo suggested that Hench focus his interest on patients with arthritis, to which he agreed (C. H. Slocumb, MD. Rheumatology at the Mayo Clinic 1926-1951. Unpublished manuscript, 1951).

Hench's initial assignment was working with the Section of Orthopedics to examine and treat patients with nonsurgical musculoskeletal conditions. In January 1926, Hench was appointed as an associate in the Rowntree Section of Medicine with a joint appointment in the Section of Orthopedics to head a new service at Saint Marys Hospital for patients with chronic arthritis (C. H. Slocumb; P. S. Hench, MD, Mayo Historical Files, Unpublished).

The new rheumatology service was established on Third Center Medical of the original Saint Marys Hospital built in 1889 (Sr M. Pantaleon, OSF. Organization of arthritic nursing services at Saint Marys Hospital, Rochester, MN. Unpublished manuscript, 1958) (Figure 1). The original hospital facilities were multiple bed wards (Figure 2). There were no modern conveniences in the original unit. Nurses walked down a long corridor to the utility room to bring water to bathe the patients. There was no separate examining room, and thus examinations were performed at the bedside. Initially, the only space available for physical therapy was a small room on the fifth floor. The room was too small to treat all patients, and on many occasions therapists carried out the exercises at the bedside (Sr M. Pantaleon, OSF).

At first, most patients seen with serious nonsurgical joint problems were admitted to the hospital service, and the new service was busy from the beginning. In 1926 there were 574 admissions (P. S. Hench, MD. Report of the arthritis service for the year 1929. Unpublished report, 1929).

In subsequent years, more patients were seen as outpatients to help reduce their expenses. However, the prac-

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FIGURE 1. Saint Marys Hospital in the 1920s. The Rheumatology Service was located on Third Floor Center between 1925 and 1941. Third Medical Center was located on the third floor above the main hospital entrance.

tice of admitting patients with multiple swollen painful joints to the Rheumatology Service at Saint Marys Hospital for work-up, rest, and physical therapy continued for many years. This was especially true the first time patients visited Mayo Clinic or when they experienced a flare-up in symptoms. In the late 1920s, the census on the hospital service averaged 30 to 40 patients (E. B. Rentschler, MD. Letter to Dr Hench. Unpublished letter, 1958). One or two internal medicine fellows (Mayo Clinic terminology for postgratudate physicians-in-training) were assigned to the rheumatology hospital service each quarter. When available, a first assistant, defined as a fellow with advanced training who had already performed a rheumatology rotation and had added responsibility, was also assigned.

To gain more experience Hench spent 6 months between October 1928 and May 1929 visiting rheumatologists in Europe, chiefly in Germany. While he was away, Dr Edwin B. Rentschler, who served as the initial first assistant, was in charge of the hospital service. In 1929, there were 348 admissions to the service and 2121 outpatient consultations, all seen by Hench and Rentschler. The Saint Marys Hospital service, which combined patient care, teaching, and clinical research, was the first academic rheumatology unit established in the United States.[7,8] For the first 10 years, Hench was the only Mayo staff member whose primary interest was in rheumatology. During that time he staffed the busy in-patient service at Saint Marys Hospital, consulted as requested on outpatients, and continued to work with orthopedic surgeons.[9,10]

From 1930 on, Hench's outpatient consulting office was located in the Vascular Section in the Plummer Building, which was completed in 1928 (N. Barker, MD. The history of the medical vascular section of the Mayo Clinic as recorded by Dr Nelson Barker, Unedited. Unpublished manuscript.) When Hench was away, Drs Barker and Edgar V. Allen of the Vascular Section took outpatient consultations for him, and a rheumatology first assistant was in charge of the hospital service (N. Barker, MD). After several years, Hench moved his outpatient office to the Orthopedic Section offices in the Plummer Building.

Dr Charles H. Slocumb came to Mayo Clinic in October 1931, after graduating from the University of Minnesota Medical School, and was appointed to the staff in 1935. Thereafter, Slocumb and Hench rotated on the rheumatology hospital service.

In 1932, Sr Mary Pantaleon was appointed head nurse on the rheumatology hospital service, a position she held for most of the next 25 years. She had worked on the service before this appointment and was knowledgeable and devoted to the care of patients with arthritis. Her interest and skills did much to make the hospital service successful

FIGURE 2. Saint Marys Hospital ward in the old hospital, which had been completed in 1889. This 5-bed ward was similar to the type of housing in the Rheumatology Service of the 1920s and 1930s.

and a leading international center for the care of patients with arthritis throughout the years.

The staff physician assigned to the hospital service was responsible for the care of all the patients on the service, regardless of who admitted the patient. He saw all the patients each morning, accompanied by the fellows on the service. Usually 2 internal medicine fellows were assigned to the hospital service and rotated call daily for work-up of new admissions. In later years, as Mayo Clinic became larger and trained more physicians, 3 internal medicine fellows were assigned to each hospital service. The fellow who admitted the patient was then responsible to monitor that patient during hospitalization. On morning rounds, the fellow assigned the day before presented the new patients to the consultant (Mayo Clinic terminology for a tenured staff physician) and others at attending rounds and suggested further tests or treatments, as needed. After the new patients were examined, rounds were made on the other patients, and updates were provided on the status of the patients. The fellows not on call for the day saw their patients in the afternoon and notified the on-call fellow of any potential problems or pending issues; they also were expected to read and study about the illnesses of their patients and rheumatology in general. The on-call physician saw all patients again in the evening and responded to any problems that occurred during the night. The consultant was available at night by telephone.

During the Great Depression, the number of patients admitted to Saint Marys Hospital service decreased. In 1930, 413 patients were admitted to the hospital service, but in 1933 the number was down to 150. By 1939, the number had risen progressively to 312. Similarly, in the early 1930s, the physicians on the hospital service were reduced to Hench or Slocumb and one fellow without a first assistant. The outpatient practice also decreased during the depression: from 2009 outpatient consultations in 1930 to 1174, the lowest, in 1932. During these times, Hench provided inpatient care in the mornings, performed outpatient consultations in the afternoons, and was also assigned to other general medical patient care duties. By 1939, with 2 staff, the outpatient consultations had increased to 3873.

During the first decades of the 20th century, the understanding of rheumatic diseases was rudimentary. As a result, it was not uncommon to classify most patients with chronic musculoskeletal conditions as having variants of a single pathologic process. Acutely infected joints with specific organisms such as staphylococci and tubercule bacilli were recognizable and separately categorized, as were gout, neuropathic arthropathy, and pulmonary osteoarthropathy. Cases of chronic swelling of multiple joints with no known

TABLE 1. **Terms Used for Rheumatoid Arthritis, Osteoarthritis, and Ankylosing Spondylitis Between 1920 and 1960**

Rheumatoid arthritis
Arthritis deformans
Chronic infectious arthritis
Chronic infectious (atrophic) arthritis
Atrophic arthritis
Proliferative arthritis
Osteoarthritis
Senescent arthritis
Hypertrophic arthritis
Osteoarthritis
Degenerative joint disease
Degenerative arthritis
Ankylosing spondylitis
Marie-Strumpell disease
Bechterew disease
Atrophic spondylitis
Rheumatoid spondylitis

cause were sometimes grouped together as "chronic polyarthritis" or "arthritis deformans."[11]

Rheumatoid Arthritis. In the 1920s, rheumatoid arthritis was called *chronic infectious arthritis*. Other terms for rheumatoid arthritis used by various authors included *proliferative arthritis* and *atrophic arthritis* (Table 1).[10] The idea that this disease was caused by a chronic infection was based on reports first by workers in Europe in the late 1800s, who found microbes in blood and joints from patients with various forms of arthritis.[12] In the United States, the report by Cecil et al[13] provided much evidence to support this theory. Using special culture techniques, they recovered streptococci from the blood of 62% of patients and the joints from 67% of patients with chronic infectious arthritis. In addition, antibodies to streptococci were found in blood. Other investigators found similar results.

As time went by, more investigators were unable to identify bacteria in blood and joints from similar patients; it was suggested that earlier findings were due to contaminants,[14] and a second variant of the chronic infection idea was advanced. This hypothesis held that toxins liberated from extra joint foci of infection caused the arthritis or, alternatively, an allergy developed to the released bacterial products and caused the arthritis.[12] Arthritis seen in patients with psoriasis and inflammatory bowel disease was suspected to have a similar pathogenesis.[10]

In the 1920s, basic treatment at Mayo Clinic for patients with chronic arthritis (probably both chronic infectious arthritis and polyarticular osteoarthritis) included a well-balanced diet, rest, and physical therapy (Table 2).[11,15] Patients with disabling arthritis were admitted to the hospital service for evaluation and initiation of therapy. They were carefully examined for foci of infection. Tonsillectomies were performed when the tonsils were enlarged or looked infected, devitalized teeth were removed, the uterine cervix was cauterized in women, and the prostate was massaged in men, although it was already recognized that improvement did not always result (C. H. Slocumb, MD).[9,15]

Physical therapy was considered important. Exercises were aimed at improving the range of motion of affected joints, strengthening muscles, and preventing deformities.[15] Heat and massage were used to improve circulation in the affected areas in an attempt to enhance removal of toxins and infection debris.[10] Joint bracing and progressive casting were used to support joints and reduce contractions, especially of the knees. Canes and shoe corrections were prescribed. In some cases of chronic arthritis of the knees, synovectomy was performed.[10] Single badly damaged joints were sometimes surgically fused.

Analgesics, including aspirin, sodium salicylate, cinchophen, and aminopyrine, were prescribed but were not considered a major aspect of therapy. In the 1920s, dilute hydrochloric acid was given orally if gastric analysis showed low acid content (C. H. Slocumb, MD). Fowler's solution (which contained potassium arsenate) was administered to some patients as a general tonic. By the early 1930s, these last 2 agents were no longer prescribed.

TABLE 2. **Treatment of Rheumatoid Arthritis Between 1920 and 1960**

Era	Treatment
1920-1940	Bed rest Balanced diet Physical therapy Patient education Salicylates, cinchophen, aminopyrine Eliminate foci of infection Vaccine therapy Fever therapy Synovectomy
1940-1950	Bed rest Balanced diet Physical therapy Patient education Salicylates Vitamins Gold therapy
1950-1960	Bed rest Balanced diet Exercise, heat, massage Patient education Salicylates Cortisone, ACTH (adrenocorticotropic hormone) Gold therapy Hydrocortisone joint injections

Weekly educational sessions that covered the nature of arthritis and treatments as then understood were held for patients and relatives.[15]

Nonspecific vaccine (protein) therapy had been introduced as a treatment in 1916 and was increasingly used in many centers during the following decade.[16] The vaccines became available through state boards of health, the US Army, and pharmaceutical companies. In addition, a number of practitioners developed their own vaccines from bacteria originally cultured from tonsils or other body sources from patients with arthritis. It was thought that using a vaccine made from cultures taken from one or more patients with chronic arthritis might be more effective because the bacteria could be directly related to the disease. A variety of bacteria were used, including strains of typhoid, staphylococci, streptococci, and others.

Vaccine therapy was used frequently at Mayo Clinic. By 1932, Hench noted that about 2500 patients had been treated with vaccine injections.[17] Approximately 1500 of these patients were on the arthritis service; 1000 patients had different conditions and were on the vascular and other services. Although many US physicians used vaccines for all types of arthritis, the Rheumatology Section at Mayo Clinic used vaccines primarily for chronic infectious arthritis. The vaccine used at Mayo Clinic was a commercial triple typhoid vaccine made from 3 strains of killed bacteria. The vaccine was usually given intravenously.[17] A prodromal period followed the injection, during which the patient might experience chills. Three to 5 hours after the injection, fever developed, and patients often experienced malaise, headache, gastrointestinal upset, and increased musculoskeletal pain. The temperature reached a maximum of 39º to 40ºC and subsided within 6 to 12 hours. A period of euphoria and reduced joint pains often followed for varying time frames.[17] Serious adverse reactions occurred, even death, but were considered uncommon. If the adverse reaction was acute and thought to be an anaphylactic reaction, epinephrine was given. If tolerated and helpful, a series of injections was given about twice a week for 6 to 10 injections. A second series could be given again after several weeks. Few if any reports on vaccine therapy contained detailed objective assessments of its effects. Vaccine use at Mayo Clinic declined toward the end of the 1930s, and eventually vaccines were no longer used.[18] One idea of the mechanism of action causing improvement in symptoms was that the vaccines desensitized patients to bacteria that might be responsible for the disease.[19] Another idea in retrospect was that the temporary improvement was an endogenous corticosteroid mediated event secondary to the stress of the vaccine injection (L. E. Ward, MD, oral communication, 2009).

During the 1920s, surgical sympathectomy was performed in selected patients with chronic infectious arthritis.[20-22] The rationale for this procedure was based on the theory that development of arthritis was influenced by a neurogenic defect that limited the circulation to involved joints. This defect was corrected, at least in part, by sympathectomy. Patients considered the most suitable for sympathectomy were young individuals with rapidly progressive arthritis. Good candidates demonstrated alterations in vasomotor activity evidenced by cold, clammy, sweaty hands and feet. Sympathectomy was also performed in patients with scleroderma and Raynaud phenomenon in an effort to improve circulation to involved areas.[23] The results were not uniform, and in the 1930s sympathectomy was limited to patients with scleroderma with Raynaud phenomenon and hypertension (L. E. Ward, MD, oral communication, 2009; C. H. Slocumb, MD).[24]

Fever therapy for arthritis was introduced in the early 1930s. The use of fever in the treatment of syphilis led to its trial in other infections, or conditions suspected of being infectious. The rationale was that an elevated temperature that killed microorganisms was tolerated by humans.[25-27] The suspected relationship of an infection, most likely streptococcal, was an important reason to try fever therapy for chronic atrophic arthritis, even though it became known that body temperatures achieved by fever therapy did not kill typical streptococci. Other possible effects included a direct bacteriostatic effect of the heat, augmentation or mobilization of antibodies against the suspected infecting organism, vasodilation that increased the blood supply to the joints and helped the body suppress the inflammation, and a general heightened metabolism caused by the fever, which was unfavorable to the suspected bacteria. In 1931, fever therapy for chronic infectious (atrophic) arthritis was reported as effective in a small number cases and was adopted during the next few years by a number of centers in the United States and elsewhere.[28,29] At Mayo Clinic, fever was induced by the Kettering hypertherm cabinet, which used electric coils and gently circulated humidified air (Figure 3).[29] The cabinet enclosed the patient in a supine position except for the head. Small sliding doors on the sides of the cabinet allowed access so that the physician or nurse could adjust protective blankets and measure blood pressure and temperature. After an hour's treatment, the patient's temperature was generally at the desired level of 40º to 41ºC, and then the hypertherm was adjusted to maintain the body temperature at the desired level for about 5 hours. Patients were encouraged to sip iced 0.6 percent saline solution during treatment to prevent salt depletion.

About 10% of patients with chronic atrophic arthritis were unable to endure the sessions of fever.[30] If the treatment was helpful, a session of fever therapy was performed twice a week for 6 to 8 treatments. A second course could be given after an interval of 2 to 3 months. Hench reviewed the Mayo Clinic results of treatment in 60 patients with

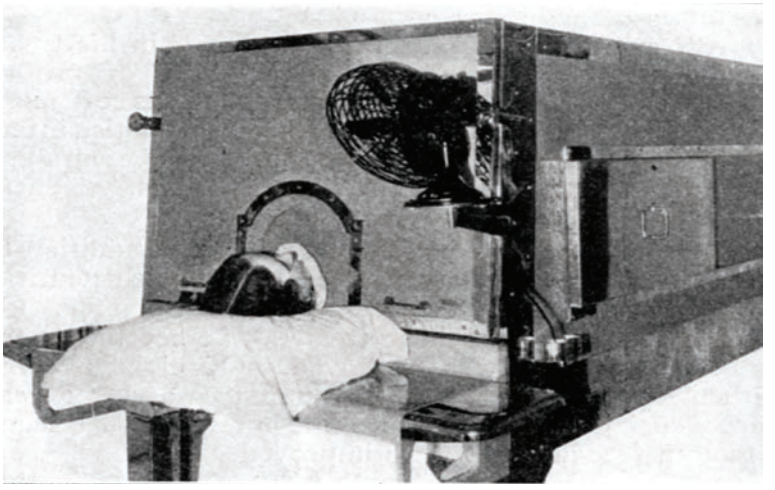

FIGURE 3. The Kettering hypertherm used for fever therapy for rheumatoid arthritis and gonococcal arthritis in the 1930s. Panel door can be seen on the right side to allow access to the patient during treatment.
From *JAMA*,[38] with permission.

chronic infectious (atrophic) arthritis in 1936. None became symptom free, but 20% had "notable improvement," 20% were moderately relieved, and the others showed no improvement.[31] The best results were obtained in patients whose duration of symptoms was less than 1 year. Any improvement tended to be of short duration. Other rheumatologists reported similar experiences. The failure to produce sustained improvement led to less use, and by the end of the 1930s fever therapy was seldom used except in occasional cases of reactive arthritis (L. E. Ward, MD, oral communication, 2009).[18,31]

By the 1930s, when the theory of systemic infection as a cause of rheumatologic diseases faded, the term *atrophic arthritis* became preferred.[14,32] Also, more attention was paid to the general condition of patients. Those unable to care for themselves adequately often became malnourished (C. H. Slocumb, MD). An appropriate diet was prescribed, and attempts were made to arrange assistance for the patient after dismissal from the hospital. After Dr Frank H. Krusen came to Mayo Clinic in 1935 to establish a Section of Physical Therapy, that part of treatment improved considerably.[5]

Gold salt injections had first been used for arthritis in France in the late 1920s.[33] Results appeared promising, and gold became used widely in Europe. Early results in the United States were not as encouraging. Toxicity was common, perhaps due to higher doses used in early studies. Slocumb noted that at one point more time was spent treating toxic reactions to gold salts and referral to Mayo Clinic than spent in treating patients with gold initiated at Mayo Clinic. In a review in 1936, Hench et al[32] noted that none of them regularly used gold therapy. However, as lower doses of gold therapy became customary, US rheumatologists revised their ideas about its use.[34,35] At Mayo Clinic, the use of gold salt injections was limited to local patients who could be followed up closely for adverse effects (C. H. Slocumb, MD).

A variety of other medications used elsewhere but not at Mayo Clinic included colloidal sulfur injections,[36] thyroid gland preparations,[37] blood transfusions,[38] radiation therapy to joints,[39] and colonic irrigations.

Osteoarthritis. *Senescent arthritis* was the common term for osteoarthritis in the 1920s. Polyarticular senescent arthritis was sometimes grouped with chronic infectious (atrophic) arthritis and was thought by some authors to be one end of the spectrum of the latter.[11,30] In the 1930s, *hypertrophic arthritis* became the preferred term.[32] *Degenerative arthritis* was also applied. Thus, in addition to being neglected by most physicians and causing much disability, the diagnosis of polyarticular senescent arthritis was often inaccurate, making assessment of any treatment difficult.

Therapy by this time included analgesics, physical measures (exercises, massage, heat applications), and braces. Many other treatments were suggested by various authors, but a conservative approach was followed at Mayo Clinic. By 1940, osteoarthritis was better understood as being distinct from rheumatoid arthritis, but little advance in therapy occurred.

Rheumatic Fever. In the 1920s, most investigators thought that rheumatic fever was related to a systemic infection because of the fever, inflamed joints, and related findings. Possible mechanisms considered were similar

to those in chronic infectious arthritis. Therapy included eradication of foci of chronic infection, including tonsillectomy. Patients were instructed to rest until all evidence of an infection had disappeared. Cardiologists recommended prolonged rest for treatment of cardiac involvement or prophylaxis against late cardiac damage. Topical oil of wintergreen and heat were applied to involved joints. Patients were treated intensively with salicylates, and the dose was increased until tinnitus or other toxic effects developed. A rapid symptomatic response generally occurred.[9]

By the late 1930s, the association of β-hemolytic streptococcal infections with acute rheumatic fever was recognized.[40,41] However, surprisingly, sulfanilamide, recently available and effective against streptococci, was not found to have an immediate beneficial effect on the active disease.[42] Its prophylactic value in preventing recurrences was eventually realized and was included in recommendations for patients.[43]

Gout. Gout was known to be related to elevated uric acid concentrations. Features important to a diagnosis of *presumptive gout* included a history of recurrent attacks in the bunion joint after trauma, surgery, or a dietary indiscretion, with complete resolution of symptoms between attacks, and absence of a cardiac murmur that might favor acute rheumatic fever. Careful search for a tophus, which could be pricked with a needle and examined microscopically for urate crystals, helped clinch the diagnosis. Radiographs of the feet or hands with tophi were often distinctive.[9,44]

Treatment of gout was symptomatic. Hot or cold packs and rest of the affected joint during the acute gouty attack were recommended. Patients were advised to start a purine-free diet with high fluid intake. Cinchophen, an analgesic and uricosuric agent, was introduced in 1910 and became widely used for gout, including at Mayo Clinic. Because acute gout appeared to be precipitated by a flare-up of a focus of infection, enlarged tonsils and dental abscesses were removed.[45]

By the 1930s, there was concern about the liver toxicity of cinchophen. Large doses of salicylates became preferred over cinchophen for uricosuric effect, and wine (tincture) of colchicum was started for acute attacks of gout.[44] Sodium bicarbonate was prescribed to increase the solubility of excreted uric acid.[46,47]

Known Specific Infections. Therapy for bacterial or fungal infections of joints was the province of orthopedics. Acute septic arthritis was treated by open drainage, traction, or fixation and often ended in ankylosis. Tuberculosis joints were often arthrodesed.[48] When sulfa drugs became available in the late 1930s, they were tried with some success in septic arthritis.[49]

Gonorrheal Septic Arthritis. The results of fever therapy were consistently better for gonorrheal septic arthritis than for chronic infectious (atrophic) arthritis. Most strains of gonococci were killed within 5 to 17 hours at 41° to 42°C.[50] Such temperatures and durations could be achieved in patients in one or more fever therapy sessions. Summarizing the literature in 1936, Hench noted that reports from various parts of the United States indicated a prompt cure rate in 80% of cases and an additional 10% chance of marked relief of symptoms. At Mayo Clinic, the usual treatment was to give 2 to 6 sessions of fever in the Kettering hypertherm at 41° to 42°C for 5 to 6 hours.[31] In a report of 9 patients with acute gonococcal arthritis so treated, 5 were promptly "cured," and the rest "markedly relieved." In 7 patients with chronic gonorrheal arthritis of more than 6 weeks' duration, 25% were cured and 45% markedly relieved.[31] Results from other centers were similar.[27,51] Later, sulfa drugs became the first choice for patients with gonococcal arthritis.[52,53]

Fibrositis. Patients with localized or generalized musculoskeletal aching without evidence of arthritis or muscle disease were grouped into the broad category of "fibrositis." Hench et al[30] estimated that 10% to 15% of the patients seen in the Mayo Rheumatology Section in the 1930s could be classified as having fibrositis. In other centers, the frequency was as high or higher.[54] Patients with localized periarticular pain and tenderness that suggested tendinitis or bursitis were grouped into the fibrositis category but also were diagnosed as having tendinitis or bursitis and treated with physical therapy and analgesics; they were sometimes referred to orthopedic surgery for operation on an area having a calcific bursitis.

Tender subcutaneous nodules were often found over the gluteal and sacroiliac areas, and these often disappeared on massage. The presence of these "fibrositic nodules" was considered diagnostically helpful. Biopsies of the nodules sometimes showed small numbers of leukocytes but often no pathologic changes.[55]

Slocumb also divided fibrositis into primary and secondary types. Primary fibrositis was a process with diffuse aching and stiffness unrelated to any other evident underlying disease. Therapy consisted of aspirin, heat, massage, rest, and avoidance of emotional stress, which was thought to be often present. These patients responded poorly to therapy but did not develop joint or muscle damage.[56] At the end of Slocumb's discussion on primary fibrositis, Hench insightfully commented that the symptoms may at times seem indefinite and vague but were

> quite consistent and sufficiently distinctive that the disease can usually be readily differentiated from 'arthritis' that the overly sympathetic or uninitiated call it, and from 'nervous exhaustion' which the unsympathetic are likely to call it.[56]

Secondary fibrositis was more severe and considered to be related to an underlying inflammatory process. A fea-

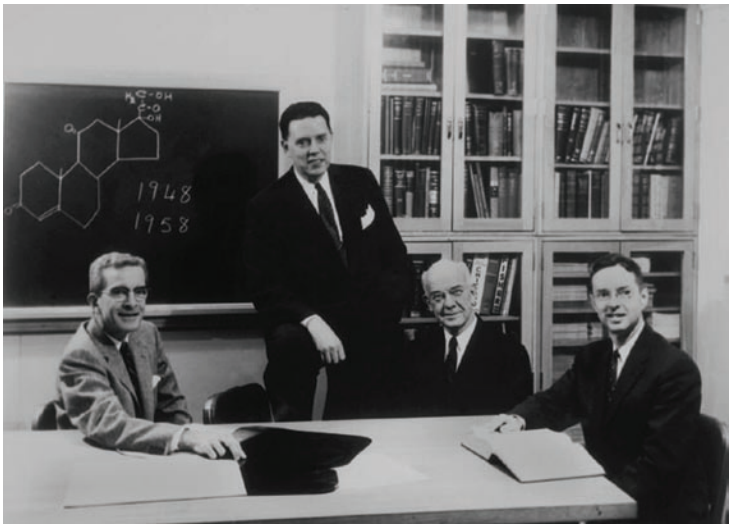

FIGURE 4. The 4 principal investigators of cortisone in rheumatic diseases shown in 1958, 10 years after the first use of the hormone in rheumatoid arthritis. From left to right, Drs Charles H. Slocumb, Phillip S. Hench, Edward C. Kendall, and Howard F. Polley.

ture of the discomfort that was helpful in diagnosis was the accentuation of the aching and stiffness in the morning, lasting a half hour or more. If an underlying disease was not identified, a diagnosis was made by exclusion. Treatment was essentially the same as for chronic infectious (atrophic) arthritis. The morning stiffness in patients with chronic infectious (atrophic) arthritis was referred to as the "fibrositic component" of the arthritis.

1940-1950

World War II was foremost in everyone's mind in the first half of the 1940s. Hench enlisted in the US Army in August 1942 and later became Chief of Medicine at the Army and Navy Hospital in Hot Springs, AR, which was designated an arthritis center. In 1940, Dr Howard F. Polley arrived at Mayo Clinic after graduating from the Ohio State University College of Medicine in 1938. He was appointed to the staff in the Section of Rheumatology in July 1943 (Figure 4).

In 1941, the Saint Marys Rheumatology Hospital Service moved from Third Medical Center in the old building to First Medical at the west end of the new Francis Building, which had been completed that year. The Rheumatology Service had its primary base at this location for more than 50 years.

A change in terminology for the 2 common forms of arthritis was adopted by the American Rheumatism Association to foster a closer relationship with the rest of the English-speaking world. The previous terms were now discarded in favor of *rheumatoid arthritis* and *osteoarthritis* (the latter also called *degenerative joint disease*).[57]

From the beginning of the establishment of the Rheumatology Section, education was an integral part of the practice. Initially, it was informal and performed on a tutorial basis on rounds through discussions and observations of findings seen in patients being examined. Later, in the 1940s, Hench developed 10 lectures on important rheumatology subjects that he gave to the internal medicine fellows during their 3-month rotation on the service (L. E. Ward, MD, oral communication, 2009). Lectures to the patients about arthritis were given weekly by a fellow or first assistant on the service.

Rheumatoid Arthritis. Patients with active polyarthritis were often admitted to the hospital service for several weeks for evaluation and treatment. Symptomatic improvement from resting most of the 24 hours of a day in bed showed patients the benefit of resting the joints and reinforced the value of continuing rest and joint protection when they left the hospital. It was believed by Mayo rheumatologists, and others as well, that rest in bed in a hospital or sanitarium for 4 to 6 weeks or longer was associated with a better outcome.[58]

Gold salt injections became more commonly used at Mayo Clinic and elsewhere in the United States in this period.[59,60] In 1947, Hench noted that serious adverse effects and mortality had greatly declined in recent years (related to smaller doses), and treatment for adverse effects had improved. He concluded that the benefits of gold injections outweighed the risks.

Other approaches around this time included trials of various vitamins.[61] Although some deficiencies likely due to malnutrition were found, replacement did not cause a beneficial effect on the arthritis.[62,63] Intravenous or intramuscular injections of foreign proteins, such as milk, horse serum, and peptone, which had been advocated at various times to "mobilize" the patient's immune system, were not used at Mayo Clinic.[64]

Rheumatoid Spondylitis. The American Rheumatism Association adopted the name *rheumatoid spondylitis* for ankylosing spondylitis. Previous terms and terms used by others included *atrophic spondylitis*, *Marie-Strumpell disease*, *Bechterew disease*, and *ankylosing spondylitis* (Table 1).[65] The Mayo Clinic staff considered spondylitis a likely variant of rheumatoid arthritis.[65-68]

Because rheumatoid spondylitis usually affects young men, it was seen by those caring for soldiers in World War II.[69] Treatment at Mayo Clinic included analgesics, postural exercises to maintain an erect spine, deep breathing exercises to maintain chest cage movement, and adequate rest in a supine position on a firm bed without a pillow to avoid kyphosis if spinal fusion occurred. Gold salt injections were not helpful.

Roentgen therapy directed to the spine and sacroiliac joints had been found to relieve back pain and stiffness.[70,71] Smith et al[72] studied its effects in 75 patients with symptomatic spondylitis; 25 were given roentgen therapy for 5 months, 25 were given sham therapy, and 25 were given no specific therapy. All were instructed to perform breathing and postural exercises. Of those receving roentgen therapy, 68% showed "notable improvement." Only about 8% in the sham therapy group or exercise therapy group showed "notable improvement." The primary improvement was in relief of pain, and less discomfort allowed patients to perform exercises better.

Rheumatic Fever. The role of an upper respiratory tract infection due to β-hemolytic streptococci in the pathogenesis of rheumatic fever was now well documented.[73] The dramatic relief of fever and joint pains afforded by salicylates was considered almost specific for the diagnosis. In the 1940s, blood salicylate concentrations could be measured, and 20 mg/dL was established at Mayo Clinic as the effective level to control the symptoms in most patients and usually was unassociated with toxicity (C. H. Slocumb, MD). A course of sulfanilamide for an infection at diagnosis was recommended, and the drug was continued in children throughout the school year as prophylaxis to reduce recurrences.[43,74] After World War II, penicillin became available and was more effective for treatment of streptococcal infections and prophylaxis than sulfa drugs.

Gout. By this time, gout was a common symptom of patients coming to Mayo Clinic. Hench[75] estimated that at least 5% of patients seen by the Mayo Clinic rheumatology staff who came for evaluation of joint disease had classic gout. Tophi were found in about 40% to 50% of all cases.[75]

Colchicine tablets replaced tincture of colchicum for acute attacks. A tablet was given hourly until the acute pain was at least "70%" better or gastrointestinal symptoms had appeared. Patients who started colchicine at the first warning of an attack could often get relief with less than the diarrheal dose. At least one study showed dietary modifications to reduce the frequency of acute attacks.[76] Interval colchicine was often prescribed to prevent acute attacks.

Because acute gout was precipitated by surgery, patients with a history of gout were given a regimen of a high carbohydrate, purine-free diet and salicylates for 5 days after a surgical operation or, alternatively, 2 or 3 colchicine tablets daily for 2 or 3 days before and after surgery. Ulcerated or infected large tophi on the hands or feet were surgically excised.

Fibrositis. Slocumb[77] expanded on the importance of distinguishing primary fibrositis from rheumatoid arthritis and psychogenic rheumatism.

In addition to previous therapies, local procaine hydrochloride injections into a painful region provided temporary relief. Other therapies tried were removal of foci of infection, autogenous vaccines, and vitamin E or alpha tocopherol. There was no objective evidence that any of these measures helped. Many cases of primary fibrositis were likely what today is called fibromyalgia. What is recognized as polymyalgia rheumatica today was categorized as secondary fibrositis in the 1940s and 1950s.

Other Rheumatic Diseases. Patients with dermatomyositis, lupus erythematosus, and scleroderma were often seen in collaboration with the dermatology and neurology departments. Very little helpful treatment was available other than salicylates for fever, pain, and other manifestations. The term *rheumaticosis* was used for a time to refer to the condition of these patients (C. H. Slocumb, MD).

The Advent of Cortisone. Hench returned from the army in January 1946. An observation that intrigued him both before and after the war was the remission in disease activity in occasional cases of rheumatoid arthritis.[78] He had noticed this particularly when young women with rheumatoid arthritis became pregnant or when patients became jaundiced. The change in course was often rapid. Hench attributed the improvement to an unknown factor, "substance X," which he thought was a hormone.

Dr Edward C. Kendall, a biochemist at Mayo Clinic who was studying the adrenal cortex, had extracted a number of substances that he named by letters of the alphabet starting with the letter "A." Some compounds had metabolic activity, such as compound E.[79] Hench was anxious to try compound E in rheumatic diseases, when it could be

obtained in adequate quantities. Compound E, later named cortisone, became available for trial in 1948 as a result of a chemical synthetic process developed by Dr Lewis H. Sarett at Merck & Co, Inc. The company agreed to supply Mayo Clinic with the drug for a trial.

The first patient to receive compound E, or cortisone, was a 28-year-old woman with severe rheumatoid arthritis. On September 21, 1948, she was given her first intramuscular injection of 100 mg of cortisone. This dose was continued daily for some days. She began to feel better by the second day, and by the third day few symptoms remained.[80] On September 28, 1948, a week after the first patient was treated, Hench left Rochester to give a lecture in London at the Heberden Society, according to a previous agreement. Thus, he was absent during the early phases of the trial.[81,82]

Because of the unexpectedly good results in the first patients, it was decided that a placebo-controlled study should be performed. Cholesterol suspensions, which looked like cortisone suspensions, were prepared by a Mayo endocrinologist who was not involved in the clinical care of the patients and was skeptical of the early results. Cholesterol or cortisone injections were assigned randomly to a series of patients with rheumatoid arthritis during the next months. The 2 clinical investigators, Slocumb and Polley, as well as the patients, were "blinded" to which injection was administered. It was easy to distinguish which patient got the cortisone injections, especially at the daily dosage of 100 mg to 300 mg. The initial report of cortisone treatment in *Mayo Clinic Proceedings* in April 1949 included results of 14 patients with moderately severe or severe rheumatoid arthritis.[80] All showed marked improvement while receiving cortisone. Two also received ACTH (adrenocorticotropic hormone), and their improvement was similar to that with cortisone.

In 1949 the effect of cortisone was evaluated in acute rheumatic fever.[83] In the first 3 patients, the symptoms of fever, tachycardia, and polyarthritis rapidly disappeared, and the erythrocyte sedimentation rate normalized, as did abnormalities on the electrocardiograms.

1950-1960

After the remarkable anti-inflammatory effects of cortisone, and also the use of ACTH in rheumatoid arthritis and rheumatic fever, other diseases were studied, including periarteritis nodosa, cranial arteritis,[84] lupus erythematosus,[85] and psoriatic arthritis.[86]

In 1950, Hench and Kendall were awarded the Nobel Prize in Physiology and Medicine "for their discoveries relating to adrenal cortical hormones, their structure and biological effects."[87] Dr Tadeus Reichstein of Switzerland, who had spent his career studying adrenal hormones, was a co-recipient. The publicity of this event and other awards increased the number of patients coming to Mayo Clinic for cortisone. As a result, the Rheumatology Section members' time was almost entirely occupied by cortisone and its uses.

Dr L. Emmerson Ward, who joined the army after graduating from Harvard Medical School, came to Mayo Clinic in 1946 and became a staff member in 1950. Ward recalled that, after cortisone therapy became available, the hospital rheumatology census increased to 40 to 45 patients, whereas it was usually about 30 patients (L. E. Ward, MD, oral communication, 2009).

In 1954, the Rheumatology Section changed its name to the Section of Rheumatology and Internal Medicine, using the nomenclature similar to most other medical specialty groups at Mayo. After this, the staff performed general physical examinations on all new rheumatology outpatients, rather than focusing only on the arthritis. General medical patients were assigned to all medical sections by rotation, depending on the number and type of patients coming to Rochester for their care. In 1954, 2141 patients were registered to the Rheumatology Section under its new status. Also, 330 patients were admitted to the Saint Marys Hospital Rheumatology Service, and 3009 were seen in consultation as outpatients, an average of 11 per working day.[88] Three additional staff were added in the 1950s: Dr John G. Mayne was appointed in July 1955, Dr Richard H. Ferguson in 1959, and Dr John W. Worthington in 1959.

Reports of the effects of cortisone and related drugs stimulated an interest in the specialty of rheumatology. The number of fellows increased, and educational programs became more structured. A weekly Clinical Case Conference was started in addition to staff lectures. At the conference, a fellow presented the medical history and physical findings in the presence of the patient. The staff and fellows could ask the patient questions, and the important physical findings were demonstrated. After the patient was returned to the ward, a discussion was held about the disease and its therapy. Polley calculated that, by the end of the 1950s, about 10% of the members of the American Rheumatism Association had trained at Mayo Clinic. On June 1, 1957, at age 61 years, Hench retired from regular Mayo Clinic staff duties

In 1958, the Section of Medicine, headed by Dr Alex E. Brown, began to participate in the care of rheumatologic patients as outpatients and on a hospital service at Rochester Methodist Hospital. Henceforth, there were 2 primary rheumatology hospital services. Worthington was assigned to this Methodist Hospital section.

Rheumatoid Arthritis. The adverse effects of cortisone in rheumatoid arthritis, as well as the beneficial effects, were quickly recognized.[89,90] In 1951, Ward et al[91] reported on the first 100 patients with rheumatoid arthritis who had received cortisone. An effective response was seen in all but one patient. To avoid adverse effects, the starting dose

was lowered. When moderate relief was attained, the dose was gradually reduced further to identify the least amount needed and to prevent adverse effects.

During the next years, a number of cortisone analogues were developed with the hope of increasing the anti-inflammatory effect and reducing the adverse effects. Prednisone and prednisolone became the glucocorticoids of choice at Mayo Clinic after studies reported in 1958 showed they were 4 to 5 times as potent as cortisone and produced less retention of sodium, chloride, and water and less excretion of potassium.[92]

Although Mayo Clinic rheumatologists began to use lower doses of glucocorticoids for rheumatoid arthritis and other diseases, many physicians in other locations continued to use larger doses. Many patients had as much morbidity from the corticosteroids as from the underlying condition. Some physicians raised the question as to the net value of cortisone and related products. Dealing with patients who were referred with hypercortisonism became a major activity of the Mayo Clinic staff (C. H. Slocumb, MD). All the rheumatology staff became deeply concerned about the frequency and extent of the adverse reactions in the patients they were seeing (L. E. Ward, MD, oral communication, 2009). In 1958, Ward et al[93] proposed guidelines for the use of prednisone in rheumatoid arthritis.

Injection of hydrocortisone and later its analogues into joints causing local symptoms was pioneered by Mayo Clinic orthopedists. Frequent injections were avoided because of concern about infections and excessive use of the injected joint after reduced pain and swelling caused by the corticosteroid.

Rheumatoid Spondylitis. Evidence had accumulated that showed that radiation treatment of rheumatoid spondylitis was followed by an increased incidence of leukemia, and its use at Mayo Clinic, although never frequent, was discontinued by the end of the 1950s.[94] Phenylbutazone, marketed in the 1950s, was used only occasionally because of adverse effects. Cortisone or prednisone was used often in the early part of that decade. Back pain and stiffness and laboratory markers of inflammation improved. Later in that period, few patients were started on any of the anti-inflammatory corticoids because of concern of adverse effects.

Osteoarthritis. In the 1950s, there was an increasing emphasis on accurate diagnosis of osteoarthritis as essential to appropriate treatment.[95] It was appreciated that many persons have mild changes of osteoarthritis on radiography, but they had no symptoms and required no medical treatment. Hydrocortisone intra-articular injections were given in one or two symptomatic joints, but with caution as in rheumatoid arthritis. In advanced cases of osteoarthritis of a single joint, arthrodesis was considered.

Rheumatic Fever. Additional experience confirmed the preliminary findings that cortisone, corticotrophin, and later prednisone rapidly suppressed the acute manifestations of rheumatic fever but did not cure it.[96] Early treatment appeared to prevent cardiac damage but did not reverse chronic valvular changes. The standard treatment program included penicillin (for a persisting streptococcal infection) and a glucocorticoid until the acute manifestations were controlled. Rheumatic fever was recognized as a self-limiting disease, and slow reduction of the cortisone dose would provide information about the length of time the drug was needed.[96] Long-term penicillin or sulfonamides were prescribed as prophylaxis against future attacks.

Gout. Although cortisone and ACTH had been found to be effective in acute gout, colchicine, both orally and intravenously, continued to be the preferred therapy. When a contraindication existed for the use of colchicine, a short course of cortisone or phenylbutazone was administered. Probenecid replaced aspirin as the uricosuric drug.[97] Sulfinpyrazone was also used after it became available in the later 1950s.

Other Rheumatic Diseases. ***Bursitis and Tendinitis.*** Hydrocortisone (originally termed *compound F*) and later similar analogues were used enterally and parenterally for joint and soft tissue, and joint injections were used for localized conditions. Dr Mark Coventry of the Orthopedic Department recalled what was probably the first injection of glucocorticoids into a joint. He was at Saint Marys Hospital one day in 1949 when Hench asked me "if I would be willing to inject cortisone into a patient with acute bursitis of the shoulder." Coventry agreed, and the next day,

> I injected the first patient with hydrocortisone. He had severe calcific tendinitis, the pain from which was uncontrollable, even with morphine, something not usually seen today. Within 14 hours after the 'compound F' was put into the area of the calcium, the patient was moving his shoulder freely.[4]

In subsequent years, many compound F injections were administered by orthopedists and by rheumatologists in similar circumstances.

Connective Tissue Disorders. Glucocorticoids became the main treatment of both lupus erythematosus and inflammatory myopathy. Although antimalarial drugs were available in the 1950s and were used elsewhere to treat connective tissue disorders, they were not used frequently in this decade at Mayo Clinic.

The first use of corticosteroids for treatment of vasculitis (including polyarteritis nodosa and temporal arteritis) was pioneered by Polley et al.[84,98]

Dr Bayard T. Horton of the Section of Medicine described temporal arteritis in the 1930s, but none of his ear-

ly patients had prominent musculoskeletal pain.[99] Perhaps this was the reason that rheumatology staff failed to connect temporal arteritis (giant cell arteritis) and secondary fibrositis (polymyalgia rheumatica) in the 1950s.

Summary and Comments

The 40-year interval of 1920 to 1960 was a period of enormous advances in the care of patients with rheumatologic disorders. Between 1920 and 1940, rest, analgesics, and physical therapy were the main helpful treatments. However, the disease advanced, and many patients developed severe joint damage and disability and were confined to a chair or bed. By 1960, numerous medications were available. The improved understanding of most rheumatic diseases fostered better management and abandonment of unhelpful or even harmful therapies. Discarding the early concept of an infectious cause of rheumatoid arthritis and related conditions made the removal of "foci of infection," vaccine, and fever therapies unnecessary.

The recognition of the connection of streptococcal infections to rheumatic fever and the introduction of sulfa drugs and penicillin were instrumental in dramatically reducing the frequency of rheumatic fever and its sequelae. The discovery of the uricosuric effect of probenecid made it possible to control many cases of gout.

The therapeutic advance of greatest impact during this time was the discovery of the powerful anti-inflammatory effects of glucocorticoids. Even with their associated adverse effects, they are still widely used today.

Not all landmark advances of the era involving Mayo Clinic physicians led immediately to new treatments. An example is the description of the lupus erythematosus (LE) cell in bone marrow and blood specimens from patients with lupus erythematosus by Hargraves et al.[100] This discovery provided an entrée to the field of autoantibodies that led to great advances in the understanding of rheumatic disease mechanisms. The presence of antinuclear antibodies in the serum of patients with many rheumatic or "autoimmune" diseases also helped align these conditions with the field of rheumatology.

Investigative methodologies progressed substantially. By 1960, clinicians expected controlled trials with placebo or sham procedures to be convinced of therapeutic efficacy of new drugs and procedures. Two examples incorporating the newer methodology mentioned herein were the sham and actual roentgen treatments in the investigation of ankylosing spondylitis and the use of placebo in the blinded early cortisone studies of rheumatoid arthritis.

Finally, in 1957, the end of the first phase of rheumatology at Mayo Clinic was marked by the retirement of Dr Hench after 34 years of practice and great accomplishments by him and his colleagues in rheumatology.

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